

REMARKS/ARGUMENTS

The Examiner is thanked for numerous helpful comments which better define the issues for response.

Claims 13-14, 17, 20-23, 34 and 40-42 stand rejected as allegedly anticipated by Grebow et al. Among the limitations of claims 13-14, 17, 20-21, 34 and 40, that are neither disclosed nor suggested by Grebow, are the requirements that total citrate be maintained in a range from 10 to 25 mM while pH is maintained in a range from 3.5 to 3.9. As established by the accompanying Declaration of Inventor William Stern (see especially the chart attached at the end thereof), the most relevant examples of Grebow formulations fail to provide this combination of citrate level and pH that is important to stability and bioavailability of the product. Grebow example 6 has too much citrate (31.25 mM citric acid and 46.26 mM sodium citrate for a total citrate concentration of 77.51 mM). Examples 7 and 10 provide compositions which are outside of the required pH range regardless of whether the sodium phosphate in these compositions is monosodium phosphate or disodium phosphate (which Grebow does not specify). Grebow neither recommends a pH within the claimed range nor specifies ingredients in the most relevant examples which would inherently produce such a pH.

The remaining claims rejected as allegedly anticipated by Grebow are method claims directed to the use of citric acid for the limited purposes of improving stability (claims 22 and 41) or bioavailability (claims 23 and 42). Grebow, however, does not mention the use of citric acid for improving bioavailability, but instead uses it as a buffer. The very wide concentration range recommended at column 11, line 44 (though slightly overlapping the range claimed in claim 22) is a very broad range that does not teach the advantage of the very narrow range of citrate which claim 22 utilizes. Grebow specifically states one line later that a higher range (0.05M to 0.2M) was preferred (Grebow column 11, lines 45-47). Accordingly, it is urged that the Examiner's rejection under 35 U.S.C. §102 over Grebow should be withdrawn.

Claims 13-14, 16-23, 34 and 40-42 stand rejected as allegedly anticipated by Kagatani et al. Among the limitations of all rejected claims that are neither disclosed nor suggested by Kagatani is the requirement that citrate concentration be from 10 to 50 mM (or an even narrower

range in some claims). As reported by the enclosed Stern declaration (see especially Table 1 attached thereto), all relevant Kagatani examples use a combination of citric acid and sodium citrate in which the citric acid alone is at too high a concentration to fall within the levels recited in the present claims, even before the further effect of additional sodium citrate is considered. Accordingly, it is urged that the anticipation rejection over Kagatani be withdrawn.

Claims 13, 14, 17, 20-23, 34 and 40-42 stand rejected as allegedly anticipated by Veronesi et al. Among the limitation of claims 13, 14, 17, 20, 21, 34 and 40 which are neither disclosed nor suggested by Veronesi is the limitation requiring citrate concentration from 10 to 25 mM. As established by the enclosed Stern Declaration (see especially Table 1) relevant examples from the Veronesi reference provide total citrate higher than this requirement of the foregoing claims. See specifically column 9 of Table 1 of the Stern Declaration wherein the lowest total citrate (which is shown as a combination of citric acid and sodium citrate in columns 5 and 8) is in excess of 30 mM. Accordingly, it is urged that the anticipation rejection over claim 13 (and all claims dependent therefrom) be withdrawn.

The remaining claims which are rejected over Veronesi are method claims directed to utilizing citric acid for improvements in bioavailability or stability. The Examiner only alleges that Veronesi uses citric acid and sodium citrate as buffers. It is not believed that Veronesi discloses or suggests the use of citric acid or sodium citrate to improve bioavailability or stability as required by claims 22 and 23 (and claims dependent from claims 22 and 23).

Claims 15, 24-28, 30-33, 35-39 and 43-44 stand rejected as allegedly obvious over the combination of Grebow and Dua. However, Dua adds only a discussion of tonicity and viscosity to the teachings of Grebow. Claims 31, 32, 37 and 38 depend from claim 13 which was already distinguished from Grebow (in the anticipation rejection above) on grounds other than tonicity or viscosity. Therefore, Dua, by addressing tonicity and viscosity, adds nothing to the deficiencies of Grebow in connection with claims 31, 32, 37 and 38. Likewise, claims 43 and 44 are dependent from claims 22 and 23 which were distinguished from Grebow (in the anticipation section above) on grounds other than tonicity and viscosity. Dua, thus, adds nothing to the deficiencies of Grebow regarding claims 43 and 44. Thus, it is urged that the obviousness

rejection over Grebow and Dua be withdrawn with respect to claims 31, 32, 37, 38, 43 and 44 for the foregoing reasons.

As to the remaining claims that are rejected over the combination of Dua and Grebow, all are believed dependent (directly or indirectly) from independent claim 15. All therefore are believed to distinguish Grebow and Dua by claim 15's recitation of "an osmotic pressure of from about 250 to about 350 mOsm/liter." Grebow is not alleged by the Examiner to discuss tonicity at all. Dua, which does discuss tonicity actually teaches against tonicity in the isotonic range recited in the rejected claims. The table at the bottom of page 237 of the Dua reference tests isotonic, hypertonic, and hypotonic formulations at both low and high viscosity. Only the isotonic formulation (300 mOsm) is within the range cited by the rejected claims. The hypertonic formulation was at 600 mOsm and the hypotonic formulation was at 100 mOsm. As reported in the Table at the bottom of page 237 of the Dua reference, the hypertonic and hypotonic formulations were taught by Dua to provide better bioavailability than the isotonic formulations at both high and low viscosity. At page 238, column 2, final sentence, Dua et al. conclude that "the bioavailability of the drug was enhanced in both the hypotonic and hypertonic condition by 4-5 fold." Dua thus suggests that tonicity outside of applicant's claimed range is preferable to tonicity within the claimed range. This teaching away by the prior art reference cannot suggest to one of skill in the art that applicants' claimed range be utilized. Therefore, it is urged that the rejection under 35 U.S.C. §103 over a combination of Grebow and Dua be withdrawn.

Finally, claims 14-15, 24-33, 35-39 and 43-44 stand rejected by the Examiner under 35 U.S.C. §103 as allegedly obvious over a combination of Kagatani and Dua. However, all rejected claims require citrate concentration lower than provided by Kagatani (see enclosed Stern Declaration, Table 1 attached thereto). Dua does not disclose or suggest any reason to alter the citrate concentration of Kagatani. Even if it were proper to combine the two references, the combination would not result in a formulation having the citrate levels required by the rejected claims. For this reason, it is urged that the obviousness rejection over a combination of Kagatani and Dua be withdrawn.

It is believed that the application is now in condition for allowance. Issuance of a Notice of Allowance is solicited.

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